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Persistent depressive symptoms and cognitive function in late midlife: the Whitehall II study

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Abstract

Objective

Depression has been widely linked to poor cognition and dementia in the elderly. However, comorbidity at older ages does not allow an assessment of the role of mental health as a risk factor for cognitive outcomes. We examined the association between depressive symptoms, measured 6 times over an 18-year period, and cognitive deficits in late midlife.

Methods

4271 men and women (35–55 years at baseline) from the Whitehall II study were followed up for 18 years during which depressive symptoms were assessed 6 times using the General Health Questionnaire depression subscale. Cognition was assessed at the most recent wave (2002–2004, mean age 61, range 50–74) using six tests: memory, reasoning, vocabulary, 2 tests of verbal fluency and the MMSE (Mini Mental State Examination). Cognitive deficit was defined as MMSE <28 and performance in the worst sex-specific quintile for the other tests.

Results

History of depressive symptoms, once or more in the 6 times assessed, had a weak association with some of the cognitive tests. However, in analysis adjusted for sociodemographic variables, diabetes, coronary heart disease, hypertension, stroke, & anti-depressant use, persistent depressive symptoms (4–6 times) were associated with cognitive deficits on all tests: memory (Odds Ratio (OR)=1.91; 95% Confidence Interval (CI)=1.36–2.67), reasoning (OR=1.60; 95% CI=1.15–2.20), vocabulary (OR=1.75; 95% CI=1.27–2.41), phonemic fluency (OR=1.40; 95% CI=1.00–1.94), semantic fluency (OR=1.68; 95% CI=1.20–2.35), and the MMSE (OR=1.76; 95% CI=1.25–2.50).

Conclusions

Our data show that depressive episodes tend to persist in some individuals and these individuals are at a greater risk of cognitive deficits in late midlife.

MESH Keywords Adult ; Aged ; Aging ; psychology ; Cognition Disorders ; complications ; diagnosis ; Depression ; complications ; diagnosis ; Female ; Follow-Up Studies ; Geriatric Assessment ; methods ; Humans ; Male ; Middle Aged ; Psychomotor Performance

Introduction

Depression¹ and impaired cognition² are common conditions in the elderly and their co-morbid prevalence doubles every five years after the age of 70, leading to both conditions being present in 25% of those over 85 years of age³. Depression has been shown to be associated with poor cognitive performance^{4–9}, cognitive decline^{10–15} and dementia^{11,16–32}. Three explanations of these associations have been put forward. The first is that depressive symptoms themselves are a psychological reaction to the awareness of declining cognitive capacities^{9,29,33}. Another implicates a common cause like vascular disease^{10,11,19,23,25,30,31}, while the third view is that depression is a risk factor for cognitive decline^{12,14,15,18,32,34,35}. This debate on depression as a cause or consequence of cognitive decline is further confused by the presence of cross-sectional, but lack of longitudinal associations, in the same studies^{6,7}.

Most of the research in this domain has been carried out on the elderly,^{5–10,12,14,16–23,26,27,29–31,35} where incipient dementia is likely to introduce some recall bias in the results. Thus, it is possible that depression is both a remote risk factor and a proximal

prodromal feature of Alzheimer's Disease (AD)³⁶. It is now widely accepted that dementia develops over many years, perhaps 20–30 years,³⁷ but much research on the identification of risk factors for dementia is undertaken in elderly populations. There is considerable evidence to link poor adult cognition to late-life dementia;³⁸ ³⁹ but few studies have looked at the association between depression and cognition at earlier ages. One exception, a small case control study on individuals aged 20 to 64 years, found major depression to be associated with deficits in memory and mental flexibility⁴. Another large study on middle aged adults, from a clinical population, used hospital admission data to show that the risk of dementia increased with the number of episodes of depressive disorders²⁸.

The temporal dimension in the association between depression and cognitive impairment⁴⁰ is crucial in order to assess whether depression, amenable to treatment, is a risk factor for cognitive outcomes. However, most studies use one measure of depression and examine cognitive function either cross-sectionally or cognitive decline prospectively. Thus, it remains unclear whether recurrent or multiple episodes of depression have a stronger effect on cognition. The primary objective of our study is to examine the association between history and frequency of depressive symptoms, measured 6 times over an 18-year period, and cognitive deficits using a range of cognitive tests in late midlife. We also examine cross-sectional associations, and associations with proximal and distal measures of depressive symptoms.

Methods

The target population for the Whitehall II study was all London-based office staff, aged 35–55 years, working in 20 civil service departments⁴¹. Baseline screening (Phase 1) took place during 1985–1988 (N=10,308; 67% men), and involved a clinical examination and a self-administered questionnaire containing sections on demographic characteristics, health, lifestyle factors, work characteristics, social support and life events. The clinical examination included measures of blood pressure, anthropometry, biochemical measurements, neuroendocrine function, and subclinical markers of cardiovascular disease. Subsequent phases of data collection have alternated between postal questionnaire alone: Phases 2 (1989–1990), 4 (1995–1996), 6 (2001) and 8 (2006) and postal questionnaire accompanied by a clinical examination: Phases 3 (1991–1993), 5 (1997–1999) and 7 (2002–2004). The University College London ethics committee approved this study.

Depressive symptoms

In the Whitehall II study a four-item depression subscale has been identified⁴² from the 30-item General Health Questionnaire (GHQ)⁴³ on the basis of factor analysis and comparison with the 7-item depression subscale of the GHQ-28⁴⁴. These items were as follows: "thinking of yourself as a worthless person", "felt life is entirely hopeless", "felt life isn't worth living", "found at times you couldn't do anything because your nerves were too bad". Depressive symptoms were assessed by summing all items scored on a Likert scale from 0–3. Respondents scoring 0–3 were considered "non-cases" and those scoring 4 or more, "GHQ depression cases". GHQ depressive symptoms were assessed at Phases 1, 2, 3, 5, 6 and 7 of the study and used to construct a summary score, range 0 to 6, indicating the number of times a person is a case. 'Distal' (to the measure of cognition) depressive symptoms were defined as GHQ depression in the first three assessments (phases 1, 2 and 3), over the first six years of follow-up. 'Proximal' (to the measure of cognition) depressive symptoms were defined as GHQ depression in the last three assessments (phases 5, 6 and 7), over the last six of the total 18-year follow-up.

Cognitive function

The cognitive test battery, administered at Phase 7 (2002–2004), consisted of six standard tasks chosen to provide a comprehensive assessment of cognitive function. The six tests are as follows:

Short-term verbal memory was assessed with a 20-word free recall test. Participants were presented a list of 20 one or two syllable words at two second intervals and were then asked to recall in writing as many of the words in any order and had two minutes to do so.

The Alice Heim 4-I (AH4-I) is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty⁴⁵. It tests inductive reasoning, measuring the ability to identify patterns and infer principles and rules. Participants had 10 minutes to do this section.

Vocabulary was assessed using the Mill Hill Vocabulary test,⁴⁶ used in its multiple format, consisting of a list of 33 stimulus words ordered by increasing difficulty and six response choices.

We used two measures of verbal fluency: phonemic and semantic⁴⁷. Phonemic fluency was assessed via "S" words and semantic fluency via "animal" words. Subjects were asked to recall in writing as many words beginning with "S" and as many animal names as they could. One minute was allowed for each test.

Finally, the 30-item Mini-Mental-State-Examination (MMSE) was used to assess global cognitive status⁴⁸.

Covariates used were age, sex, highest qualification on leaving full-time education (primary school, lower secondary school, higher secondary school, university, and higher university degree) and marital status (married/cohabiting, single, widowed, and

divorced/separated). As measures of health are associated with depression and cognition,^{31 40} we adjusted for the effects of diabetes (self-report of doctor diagnosis), clinically validated Coronary Heart Disease (CHD), stroke (self-report of doctor diagnosis) and hypertension (systolic and diastolic blood pressure >140/90 mm/Hg or treatment for hypertension). Anti-depressant use was assessed using a questionnaire on medications.

Statistical analysis

Scores in the lowest sex-specific quintile for all tests except the MMSE were seen to represent cognitive deficit. Among men (women), deficit was defined as scores below 5 (5) for memory, 39 (30) for the AH4-I, 24 (20) for the Mill-Hill, 13 (12) for phonemic fluency, and 13 (12) for semantic fluency. For the MMSE, instead of applying the standard cut off used in elderly populations, we used a higher cut-off of 28 in order to match the categorisation for other cognitive tests, leading to 12.1% men and 14.7% women to be classified as having cognitive deficit.

We first examined the association between GHQ depression and cognitive deficit using the broad categorization of those with and without a history of depressive symptoms at Phase 7. Thus, depression “caseness” at any phase over the 18-year follow-up led the individual to be classified as having a history of GHQ depression. These associations were assessed using logistic regression, first adjusted for age, sex, marital status and education in order to remove confounding effects of socio-demographic variables. The second level of adjustment includes measures of diabetes, CHD, hypertension, stroke and anti-depressant use in order to assess whether the association between depression and cognition was robust to adjustment for potential common causes ^{10 ;11 ;19 ;23 ;25 ;30 ;31} and confounding by antidepressant use. We repeated this analysis using data only from Phase 7 in order to assess the cross-sectional association between GHQ depression and cognitive deficit.

We then examined the association between frequency of depressive symptoms over the 18-year follow-up and cognitive deficit at Phase 7. For these analyses we categorized the six measures of GHQ depression as following: never depressed, depressed once, depressed 2–3 times and depressed 4–6 times. Subsequently we examined the association between ‘distal’ and ‘proximal’ depressive symptoms and poor cognitive performance. For both these measures we categorised proximal and distal depressive symptoms as following: never depressed, depressed once, and depressed 2–3 times. All analyses have the two levels of adjustment outlined above, the first for the socio-demographic variables and the second for potential common causes. All analyses were performed using SAS statistical software, version 9.1.

RESULTS

Of the 10,308 participants at the start of the Whitehall II study, 6967 were alive and involved in the study at Phase 7. Of these, 5837 undertook cognitive testing and for 4353 individuals a full history of GHQ depression (measured 6 times over 18 years) was available. Data on covariates were missing for a further 82 individuals, leading to the analysis on 4271 participants. Compared to baseline, more men (72% vs. 67%) and more participants with a university degree or higher (30% vs. 27%) were included in our analyses. Out of the 4271 participants, a similar number reported experiencing depressive symptoms at all six measures: 11.9%, 13.8%, 12.1%, 11.4%, 9.6% and 10.9%, respectively.

Table 1 compares those with a history of depressive symptoms, GHQ depression at one or more of the 6 phases, with those who did not report depressive symptoms at any of the 6 measures over the 18-year period. Those with a history of depression were more likely to be unmarried, highly educated and on anti-depressants. The interaction term between sex and the summary score of depressive symptoms showed no sex differences on the influence of depression on cognition (all $p>0.13$) thus men and women were combined in further analysis. Table 2 presents the results from the logistic regression showing the association between history of depressive symptoms, defined as GHQ depression at any of the 6 measures, and cognitive deficit on the left hand side. On the right hand side are shown the cross-sectional associations between depressive symptoms and cognitive deficit at Phase 7. In general terms, the associations between depressive symptoms and cognitive deficit are stronger in cross-sectional analyses.

The association between the frequency of GHQ depression, measured 6 times over 18 years, and poor cognitive performance are shown in Table 3 . The categories depressed 2 (6.9%) and 3 times (3.9%) were combined in these analyses. Similarly, the categories depressed 4 (2.9%), 5 (1.7%) and 6 times (1.2%) were also combined. Frequent depressive symptoms (4 to 6 times) were associated with poor performances on the tests of memory compared to participants who report no depressive symptoms at any of the 6 measures over the 18-year follow-up (Odds Ratio (OR)=1.91; 95% Confidence Interval (CI)=1.36–2.67), reasoning (OR=1.60; 95% CI=1.15–2.20), vocabulary (OR=1.75; 95% CI=1.27–2.41), phonemic fluency (OR=1.40; 95% CI=1.00–1.94), semantic fluency (OR=1.68; 95% CI=1.20–2.35), and the MMSE (OR=1.76; 95% CI=1.25–2.50).

Table 4 presents the results on the association between ‘distal’ depressive symptoms, GHQ depression in the three measures taken during the first 6 years of follow-up, and poor cognitive performance. Those with 2 (6.4%) and 3 episodes (3.3%) of GHQ depression have been combined in these analyses. There is some evidence of an association between frequent (2–3 times out of the 3 measured) distal

depressive symptoms and poor memory (OR=1.49; 95% CI=1.14–1.95) and semantic fluency (OR=1.35; 95% CI=1.03–1.76). Table 5 presents the results for ‘proximal’ depressive symptoms, depressive symptoms in the 6 years before the measure of cognition. Here again, two (4.3%) and three (3.6%) episodes of depression have been combined for the analyses. Frequent ‘proximal’ depressive symptoms (2–3 times out of the 3 measured) was associated with poor performance on all tests (ORs 1.5 to 1.8 for the tests).

DISCUSSION

A quick look at our results would suggest that the association between depressive symptoms and cognitive deficit in late midlife is being driven by cross-sectional associations. However, this interpretation does not take into account the fact that depressive episodes tend to cluster in individuals. 49% of those with (distal) GHQ depression at Phases 1, 2 or 3 also had (proximal) depressive symptoms at Phases 5, 6 or 7. Furthermore, 43% of those with 2–3 episodes of ‘distal’ depressive symptoms also had 2–3 episodes of ‘proximal’ depressive symptoms. The persistence effect is stronger when looking at all 6 measures of GHQ depression over the 18-year period. In all, 250 participants reported depressive episodes between 4 and 6 times over the total follow-up period; out of these 210 (84%) had 2–3 episodes of ‘distal’ and 218 (87%) reported ‘proximal’ depressive symptoms. Thus, clearly a subgroup of individuals report persistent depressive symptoms and our results suggest that it is this group that has greater risk of cognitive deficits in late midlife.

The association between depressive symptoms and cognition, impaired cognition or dementia has been much examined in the research literature. There is a general consensus that it is important to examine the temporal aspect of this association in order to make sense of the three different explanations of this association: depression as a cause or a consequence of cognitive decline, plus the common cause hypothesis. Considerable attention has been paid to separating the cross-sectional from the longitudinal associations^{6 ;7} and examining either multiple waves of data on cognition^{10 –14} or dementia^{16 –31}. Less attention has been paid to measuring depression over the adult lifecourse. The exceptions are studies that assess history of depression^{20 ;27 ;28 ;49 ;49}. However, two of these studies measure depression history retrospectively, ^{24 ;27} and are likely to suffer from some recall bias, particularly as they are based on the elderly. The other two studies use medical data to show increased risk of cognitive deficit with increases in the number of episodes of depressive disorders²⁸ or with recurrent depression⁴⁹. One of these used data on hospital admissions for affective disorders²⁸ and the other was on an elderly sample and used data drawn from physician records⁴⁹.

A recent meta-analysis examined the association between depression and Alzheimer’s disease (AD) and reported an OR of 2.02 (95% CI=1.80–2.26) for AD among those with a history of depression³⁶. The review also found a positive association between a longer interval between the diagnosis of depression and an increased risk of AD, in the few studies where it was available. The conclusion reached by the review was that depression appears to be a risk factor rather than a prodrome of AD. However, subsequent work continues to show inconsistent results. Data from the Rush Religious Orders Study⁵⁰ and the Rotterdam Scan study³⁵ suggest no increase in depressive symptoms during the prodromal phase of dementia but a Swedish Twin study found the contrary.⁵¹ Finally, another study found only “severe” depression to be a risk factor for dementia.³² However, in studies on the elderly, when the risk factor being examined is influenced by early subclinical stages of disease, protopathic bias is a real concern. Studies like ours that shift the observation window to midlife are likely to be unbiased in this regard. Our results suggest that multiple or persistent episodes of depressive symptoms are associated with greater risk of cognitive deficits. The association of frequent proximal depressive episodes with cognition was somewhat more robust than that with frequent distal depressive episodes. However, in further analyses (not shown but available on request) we excluded all individuals with distal episodes and the associations for proximal episodes were much reduced. Thus, clearly it is persistent depressive symptoms that are either a risk factor or identify a group of individuals at risk of cognitive deficits.

Of the studies examining dementia as an outcome, a majority have focussed on AD^{11 ;17 ;21 ;22 ;24 –27 ;29 ;30 ;36}, which implicates deficits in memory^{38 ;39}. Our results suggest a consistent effect of depressive symptoms (history, cross-sectional, distal, proximal and overall frequency) on memory deficits. One study on the elderly reported recurrent depression or history of depression to be characterized by deficits in memory⁴⁹, suggesting that memory might be particularly vulnerable domain. However, another study in which depressive symptoms were associated with an increased risk of mild cognitive impairment (MCI) showed stronger effects for the MCI subtype without memory impairment¹⁵. In general terms, the mechanisms behind the association between depression and cognition remain little understood. It has been suggested that the link between depression and cognition can be attributed to vascular disease^{10 ;11 ;19 ;23 ;25 ;30 ;31}, reflecting the common cause hypothesis. In our data, as in other studies,⁵² statistical adjustment for vascular disease did not much change the association between persistent depressive symptoms and cognitive deficit.

Our study has several strengths and limitations. The strengths lie in the size of the study; the 6 measures of depressive symptoms over 18 years and multiple measures of cognition. A further strength is the examination of the link between depression and cognition in an age-group where incipient dementia is less likely to be a confounding factor. The limitations are mostly to do with the scale used to assess depression. The GHQ depression scale used is only a part of the seven item depression scale of the GHQ 28. GHQ depression is also best considered to be a measure of depressive symptoms, and should not be equated with clinically diagnosed depression⁴². It is essentially a measure of self-reported depressive symptoms and although reliable, it does not indicate the severity of depression. There is some evidence to suggest that major depression has a stronger effect on cognitive impairment^{4 ;32}. Nevertheless, our six measures of

depressive symptoms are a good measure of persistent depression. A further limitation is that no data were available for cognition at baseline and thus it remains unclear to what extent cognitive functioning at study entry determined subsequent trajectories of depression. Finally, the Whitehall II study is based on white-collar civil servants and is not representative of the general population, limiting the generalisability of our results.

In conclusion, our study of middle-aged adults from the Whitehall II cohort shows that persistent depressive symptoms are a risk factor for cognition in late midlife. This association is independent of vascular risk factors and appears to implicate memory in particular. Of the three hypotheses put forward to explain the association between depression and cognition – depression as a cause or a consequence and the common cause hypothesis – we did not examine the hypothesis that depression was a consequence of declining cognition. However, there was little evidence of vascular diseases explaining away the association between persistent depressive symptoms and cognition. Our results suggest an association between persistent depressive symptoms and poor cognitive function in late midlife. However, whether this association is causal remains unclear as the precise mechanisms linking depression to cognitive functioning remain to be elucidated.

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References:

Reference List

1. Denihan A, Kirby M, Bruce I, Cunningham C, Coakley D, Lawlor BA. Three-year prognosis of depression in the community-dwelling elderly. *Br J Psychiatry*. 2000; 176 : 453 - 457
2. Ritchie K, Lovestone S. The dementias. *Lancet*. 2002; 360 : 1759 - 1766
3. Arve S, Tilvis RS, Lehtonen A, Valvanne J, Sairanen S. Coexistence of lowered mood and cognitive impairment of elderly people in five birth cohorts. *Aging (Milano)*. 1999; 11 : 90 - 95
4. Airaksinen E, Larsson M, Lundberg I, Forsell Y. Cognitive functions in depressive disorders: evidence from a population-based study. *Psychol Med*. 2004; 34 : 83 - 91
5. Bierman EJ, Comijs HC, Jonker C, Beekman AT. Effects of anxiety versus depression on cognition in later life. *Am J Geriatr Psychiatry*. 2005; 13 : 686 - 693
6. Dufouil C, Fuhrer R, Dartigues JF, Alperovitch A. Longitudinal analysis of the association between depressive symptomatology and cognitive deterioration. *Am J Epidemiol*. 1996; 144 : 634 - 641
7. Ganguli M, Du Y, Dodge HH, Ratcliff GG, Chang CC. Depressive symptoms and cognitive decline in late life: a prospective epidemiological study. *Arch Gen Psychiatry*. 2006; 63 : 153 - 160
8. Rabbitt P, Donlan C, Watson P, McInnes L, Bent N. Unique and interactive effects of depression, age, socioeconomic advantage, and gender on cognitive performance of normal healthy older people. *Psychol Aging*. 1995; 10 : 307 - 313
9. Vinkers DJ, Gussekloo J, Stek ML, Westendorp RG, van der Mast RC. Temporal relation between depression and cognitive impairment in old age: prospective population based study. *BMJ*. 2004; 329 : 881 -
10. Bassuk SS, Berkman LF, Wypij D. Depressive symptomatology and incident cognitive decline in an elderly community sample. *Arch Gen Psychiatry*. 1998; 55 : 1073 - 1081
11. Geerlings MI, Schoevers RA, Beekman AT. Depression and risk of cognitive decline and Alzheimer's disease. Results of two prospective community-based studies in The Netherlands. *Br J Psychiatry*. 2000; 176 : 568 - 575
12. Paterniti S, Verdier-Taillefer MH, Dufouil C, Alperovitch A. Depressive symptoms and cognitive decline in elderly people. Longitudinal study. *Br J Psychiatry*. 2002; 181 : 406 - 410
13. Wilson RS, Mendes de Leon CF, Bennett DA, Bienias JL, Evans DA. Depressive symptoms and cognitive decline in a community population of older persons. *J Neurol Neurosurg Psychiatry*. 2004; 75 : 126 - 129
14. Yaffe K, Blackwell T, Gore R, Sands L, Reus V, Browner WS. Depressive symptoms and cognitive decline in nondemented elderly women: a prospective study. *Arch Gen Psychiatry*. 1999; 56 : 425 - 430
15. Ravaglia G, Forti P, Lucicesare A. Prevalent depressive symptoms as a risk factor for conversion to mild cognitive impairment in an elderly Italian cohort. *Am J Geriatr Psychiatry*. 2008; 16 : 834 - 843
16. Baldwin RC, Gallagher A, Gourlay M, Jackson A, Burns A. Prognosis of late life depression: a three-year cohort study of outcome and potential predictors. *Int J Geriatr Psychiatry*. 2006; 21 : 57 - 63
17. Andersen K, Lolk A, Kragh-Sorensen P, Petersen NE, Green A. Depression and the risk of Alzheimer disease. *Epidemiology*. 2005; 16 : 233 - 238
18. Buntinx F, Kester A, Bergers J, Knottnerus JA. Is depression in elderly people followed by dementia? A retrospective cohort study based in general practice. *Age Ageing*. 1996; 25 : 231 - 233
19. Chen P, Ganguli M, Mulsant BH, DeKosky ST. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. *Arch Gen Psychiatry*. 1999; 56 : 261 - 266
20. Cooper B, Holmes C. Previous psychiatric history as a risk factor for late-life dementia: a population-based case-control study. *Age Ageing*. 1998; 27 : 181 - 188
21. Dal Forno G, Palermo MT, Donohue JE, Karagiozis H, Zonderman AB, Kawas CH. Depressive symptoms, sex, and risk for Alzheimer's disease. *Ann Neurol*. 2005; 57 : 381 - 387
22. Devanand DP, Sano M, Tang MX. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Arch Gen Psychiatry*. 1996; 53 : 175 - 182
23. Fuhrer R, Dufouil C, Dartigues JF. Exploring sex differences in the relationship between depressive symptoms and dementia incidence: prospective results from the PAQUID Study. *J Am Geriatr Soc*. 2003; 51 : 1055 - 1063
24. Green RC, Cupples LA, Kurz A. Depression as a risk factor for Alzheimer disease: the MIRAGE Study. *Arch Neurol*. 2003; 60 : 753 - 759

- 25 . Heun R , Kockler M , Ptok U . Depression in Alzheimer's disease: is there a temporal relationship between the onset of depression and the onset of dementia? . *Eur Psychiatry* . 2002 ; 17 : 254 - 258
- 26 . Holtzer R , Scarmeas N , Wegesin DJ . Depressive symptoms in Alzheimer's disease: natural course and temporal relation to function and cognitive status . *J Am Geriatr Soc* . 2005 ; 53 : 2083 - 2089
- 27 . Jorm AF , van Duijn CM , Chandra V . Psychiatric history and related exposures as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group . *Int J Epidemiol* . 1991 ; 20 : (Suppl 2) S43 - S47
- 28 . Kessing LV , Andersen PK . Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? . *J Neurol Neurosurg Psychiatry* . 2004 ; 75 : 1662 - 1666
- 29 . Migliorelli R , Teson A , Sabe L , Petracchi M , Leiguarda R , Starkstein SE . Prevalence and correlates of dysthymia and major depression among patients with Alzheimer's disease . *Am J Psychiatry* . 1995 ; 152 : 37 - 44
- 30 . Steffens DC , Plassman BL , Helms MJ , Welsh-Bohmer KA , Saunders AM , Breitner JC . A twin study of late-onset depression and apolipoprotein E epsilon 4 as risk factors for Alzheimer's disease . *Biol Psychiatry* . 1997 ; 41 : 851 - 856
- 31 . Wilson RS , Barnes LL , Mendes de Leon CF . Depressive symptoms, cognitive decline, and risk of AD in older persons . *Neurology* . 2002 ; 59 : 364 - 370
- 32 . Chen R , Hu Z , Wei L , Qin X , McCracken C , Copeland JR . Severity of depression and risk for subsequent dementia: cohort studies in China and the UK . *Br J Psychiatry* . 2008 ; 193 : 373 - 377
- 33 . Solfrizzi V , D'Introno A , Colacicco AM . Incident occurrence of depressive symptoms among patients with mild cognitive impairment - the Italian longitudinal study on aging . *Dement Geriatr Cogn Disord* . 2007 ; 24 : 55 - 64
- 34 . Sachs-Ericsson N , Joiner T , Plant EA , Blazer DG . The influence of depression on cognitive decline in community-dwelling elderly persons . *Am J Geriatr Psychiatry* . 2005 ; 13 : 402 - 408
- 35 . Geerlings MI , den HT , Koudstaal PJ , Hofman A , Breteler MM . History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease . *Neurology* . 2008 ; 70 : 1258 - 1264
- 36 . Ownby RL , Crocco E , Acevedo A , John V , Loewenstein D . Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis . *Arch Gen Psychiatry* . 2006 ; 63 : 530 - 538
- 37 . Alzheimer's Disease International . World Alzheimer Report . 2009 ; Ref Type: Online Source
- 38 . Petersen RC , Doody R , Kurz A . Current concepts in mild cognitive impairment . *Arch Neurol* . 2001 ; 58 : 1985 - 1992
- 39 . Morris JC , Storandt M , Miller JP . Mild cognitive impairment represents early-stage Alzheimer disease . *Arch Neurol* . 2001 ; 58 : 397 - 405
- 40 . Barnes DE , Alexopoulos GS , Lopez OL , Williamson JD , Yaffe K . Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study . *Arch Gen Psychiatry* . 2006 ; 63 : 273 - 279
- 41 . Marmot MG , Smith GD , Stansfeld S . Health inequalities among British civil servants: the Whitehall II study . *Lancet* . 1991 ; 337 : 1387 - 1393
- 42 . Stansfeld SA , North FM , White I , Marmot MG . Work characteristics and psychiatric disorder in civil servants in London . *J Epidemiol Community Health* . 1995 ; 49 : 48 - 53
- 43 . Goldberg DP . The detection of psychiatric illness by questionnaire . 1972 ; London, UK Oxford University Press ; Ref Type: Serial (Book, Monograph)
- 44 . Goldberg DP , Hillier VF . A scaled version of the General Health Questionnaire . *Psychol Med* . 1979 ; 9 : 139 - 145
- 45 . Heim AW . AH 4 group test of general Intelligence . Windsor, UK NFER-Nelson Publishing Company Ltd ; 1970 ;
- 46 . Raven JC . Guide to using the Mill Hill vocabulary test with progressive matrices . London, UK HK Lewis ; 1965 ;
- 47 . Borkowski JG , Benton AL , Spreen O . Word fluency and brain damage . *Neuropsychologica* . 1967 ; 5 : 135 - 140
- 48 . Folstein MF , Folstein SE , McHugh PR . "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician . *J Psychiatr Res* . 1975 ; 12 : 189 - 198
- 49 . Rapp MA , Dahlman K , Sano M , Grossman HT , Haroutunian V , Gorman JM . Neuropsychological differences between late-onset and recurrent geriatric major depression . *Am J Psychiatry* . 2005 ; 162 : 691 - 698
- 50 . Wilson RS , Arnold SE , Beck TL , Bienias JL , Bennett DA . Change in depressive symptoms during the prodromal phase of Alzheimer disease . *Arch Gen Psychiatry* . 2008 ; 65 : 439 - 445
- 51 . Brommelhoff JA , Gatz M , Johansson B , McArdle JJ , Fratiglioni L , Pedersen NL . Depression as a risk factor or prodromal feature for dementia? Findings in a population-based sample of Swedish twins . *Psychol Aging* . 2009 ; 24 : 373 - 384
- 52 . Luchsinger JA , Honig LS , Tang MX , Devanand DP . Depressive symptoms, vascular risk factors, and Alzheimer's disease . *Int J Geriatr Psychiatry* . 2008 ; 23 : 922 - 928

Table 1

Sample characteristics at Phase 7 of those with those with and without a history of depressive symptoms.

	MEN			WOMEN		
	Ever depressed †	Never depressed †	P	Ever depressed †	Never depressed †	P
	N=965 (31.4%)	N=2111 (68.6%)		N=454 (38.0%)	N=741 (62.0%)	
Age (M (SD))	60.4 (5.9)	61.4 (6.0)	<0.0001	61.1 (6.0)	61.5 (6.2)	0.37
% Married	757 (78.5 %)	1820 (86.2 %)	<0.0001	238 (52.4 %)	443 (59.8 %)	0.01
% University degree or higher	347 (36.0 %)	658 (31.2 %)	0.009	121 (26.7 %)	141 (19.0 %)	0.002
% Coronary Heart Disease	94 (9.7 %)	204 (9.7 %)	0.94	38 (8.4 %)	57 (7.7 %)	0.67
% Diabetes	221 (22.9 %)	529 (25.1 %)	0.20	98 (21.6 %)	180 (24.3 %)	0.28
% Hypertension	365 (37.8 %)	809 (38.3 %)	0.80	159 (35.0 %)	315 (42.5 %)	0.01
% Stroke	32 (3.3 %)	58 (2.8 %)	0.38	10 (2.2 %)	15 (2.0%)	0.83
% Anti-depressant medication	58 (6.0 %)	26 (1.2 %)	<0.0001	34 (7.5 %)	18 (2.4 %)	<0.0001

† Depressed one or more times over the 6 waves of measurement.

‡ Not depressed at any of the 6 measures over the 18-year follow-up.

M mean, SD standard deviation.

Table 2

Association between depressive symptoms (history, and cross-sectionally) and cognitive deficit[†] at Phase 7.

	History of depressive symptoms and cognition		Cross-sectional association between depressive symptoms and cognition	
	Never Depressed [‡]	Ever (once or more Depressed)	Not Depressed at Phase 7	Depressed at Phase 7
	N=2852 (66.8%)	N=1419 (33.2%)	N=3805 (89.1%)	N=466 (10.9%)
	OR (95% CI)		OR (95% CI)	
Memory				
adjusted for age, sex, marital status & education	1	1.20 (1.00–1.45)*	1	1.38 (1.06–1.80)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.19 (0.99–1.43)	1	1.36 (1.04–1.77)*
AH4-I (reasoning)				
adjusted for age, sex, marital status & education	1	1.26 (1.07–1.49)*	1	1.46 (1.14–1.86)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.28 (1.08–1.51)*	1	1.46 (1.14–1.87)*
Mill Hill (vocabulary)				
adjusted for age, sex, marital status & education	1	1.14 (0.96–1.34)	1	1.40 (1.10–1.78)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.14 (0.96–1.35)	1	1.39 (1.10–1.77)*
Phonemic fluency				
adjusted for age, sex, marital status & education	1	1.11 (0.94–1.32)	1	1.24 (0.97–1.60)
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.11 (0.94–1.32)	1	1.22 (0.94–1.58)
Semantic fluency				
adjusted for age, sex, marital status & education	1	1.19 (1.00–1.42)*	1	1.40 (1.10–1.80)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.19 (1.00–1.42)*	1	1.37 (1.05–1.77)*
MMSE				
adjusted for age, sex, marital status & education	1	1.08 (0.89–1.32)	1	1.24 (0.93–1.64)
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.05 (0.86–1.29)	1	1.17 (0.88–1.56)

[†] Worst sex-specific quintile of cognitive function at Phase 7; covariates drawn from Phase 7.

[‡] Not depressed at any of the 6 measures over the 18-year follow-up.

Table 3The association between frequency of depressive symptoms over 18 years and cognitive deficit[†] at phase 7.

	Never Depressed [‡] N=2852 (66.8%)	Depressed 1 time N=706 (16.5%)	Depressed 2 or 3 times N=463 (10.8%)	Depressed 4, 5 or 6 times N=250 (5.9%)
	ref	OR (95% CI)	OR (95% CI)	OR (95% CI)
Memory				
adjusted for age, sex, marital status & education	1	0.95 (0.74–1.22)	1.27 (0.96–1.67)	1.92 (1.38–2.66)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	0.95 (0.74–1.22)	1.26 (0.96–1.66)	1.91 (1.36–2.67)*
AH4-I (reasoning)				
adjusted for age, sex, marital status & education	1	1.16 (0.93–1.44)	1.26 (0.98–1.63)	1.60 (1.16–2.20)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.18 (0.95–1.47)	1.28 (0.99–1.66)	1.60 (1.15–2.20)*
Mill Hill (vocabulary)				
adjusted for age, sex, marital status & education	1	1.08 (0.87–1.34)	0.93 (0.72–1.22)	1.75 (1.28–2.40)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.10 (0.88–1.36)	0.94 (0.72–1.23)	1.75 (1.27–2.41)*
Phonemic fluency				
adjusted for age, sex, marital status & education	1	1.06 (0.85–1.33)	1.04 (0.80–1.36)	1.43 (1.03–1.98)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.07 (0.86–1.34)	1.04 (0.80–1.37)	1.40 (1.00–1.94)*
Semantic fluency				
adjusted for age, sex, marital status & education	1	1.01 (0.80–1.28)	1.21 (0.93–1.60)	1.73 (1.25–2.40)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.03 (0.81–1.30)	1.22 (0.93–1.60)	1.68 (1.20–2.35)*
MMSE				
adjusted for age, sex, marital status & education	1	0.95 (0.73–1.23)	0.91 (0.66–1.25)	1.90 (1.35–2.65)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	0.95 (0.73–1.23)	0.89 (0.65–1.23)	1.76 (1.25–2.50)*

[†] Worst sex-specific quintile of cognitive function; covariates drawn from Phase 7.[‡] Not depressed at any of the 6 measures over the 18-year follow-up.

Table 4

The association between frequency of DISTAL depressive symptoms (Phases 1, 2, 3) and cognitive deficit[†] at phase 7.

	Not Depressed [‡]	Depressed 1 time	Depressed 2 or 3 times
	N=3208 (75.1%)	N=651 (15.2%)	N=412 (9.7%)
		OR (95% CI)	OR (95% CI)
Memory			
adjusted for age, sex, marital status & education	1	1.14 (0.90–1.45)	1.50 (1.14–1.97)*
+ diabetes, CHD & hypertension		1.14 (0.90–1.46)	1.49 (1.14–1.95)*
AH4-I (reasoning)			
adjusted for age, sex, marital status & education	1	1.13 (0.90–1.40)	1.22 (0.94–1.58)
+ diabetes, CHD & hypertension		1.14 (0.91–1.42)	1.20 (0.92–1.56)
Mill Hill (vocabulary)			
adjusted for age, sex, marital status & education	1	1.16 (0.93–1.45)	1.06 (0.81–1.39)
+ diabetes, CHD & hypertension	1	1.17 (0.94–1.46)	1.05 (0.80–1.37)
Phonemic fluency			
adjusted for age, sex, marital status & education	1	0.93 (0.74–1.17)	1.21 (0.93–1.57)
+ diabetes, CHD & hypertension	1	0.93 (0.74–1.18)	1.19 (0.92–1.56)
Semantic fluency			
adjusted for age, sex, marital status & education	1	1.20 (0.95–1.51)	1.36 (1.04–1.78)*
+ diabetes, CHD & hypertension	1	1.21 (0.96–1.52)	1.35 (1.03–1.76)*
MMSE			
adjusted for age, sex, marital status & education	1	0.97 (0.74–1.26)	1.31 (0.98–1.76)
+ diabetes, CHD & hypertension	1	0.98 (0.74–1.28)	1.29 (0.96–1.73)

[†] Worst sex-specific quintile of cognitive function at Phase 7; covariates drawn from Phase 3.

[‡] Not depressed at the 3 distal measures of depressive symptoms.

Table 5

The association between frequency of PROXIMAL depressive symptoms (Phases 5, 6, 7) and cognitive deficit[†] at phase 7.

	Not Depressed	Depressed 1 time	Depressed 2 or 3 times
	N=3399 (79.6%)	N=535 (12.5%)	N=337 (7.9%)
		OR (95% CI)	OR (95% CI)
Memory			
adjusted for age, sex, marital status & education	1	1.13 (0.87–1.48)	1.74 (1.30–2.34)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.12 (0.86–1.47)	1.70 (1.26–2.29)*
AH4-I (reasoning)			
adjusted for age, sex, marital status & education	1	1.30 (1.02–1.64)*	1.75 (1.33–2.30)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.30 (1.03–1.66)*	1.76 (1.32–2.33)*
Mill Hill (vocabulary)			
adjusted for age, sex, marital status & education	1	1.20 (0.95–1.52))	1.58 (1.20–2.09)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.20 (0.95–1.52)	1.57 (1.18–2.08)*
Phonemic fluency			
adjusted for age, sex, marital status & education	1	1.09 (0.85–1.39)	1.51 (1.14–2.00)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.08 (0.84–1.39)	1.48 (1.11–1.98)*
Semantic fluency			
adjusted for age, sex, marital status & education	1	0.95 (0.73–1.24)	1.80 (1.36–2.39)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	0.95 (0.73–1.24)	1.76 (1.32–2.36)*
MMSE			
adjusted for age, sex, marital status & education	1	1.03 (0.77–1.37)	1.70 (1.25–2.31)*
+ diabetes, CHD, hypertension, stroke, & anti-depressant use	1	1.00 (0.75–1.34)	1.59 (1.16–2.18)*

[†] Worst sex-specific quintile of cognitive function at Phase 7; covariates drawn from Phase 7.

[‡] Not depressed at the 3 proximal measures of depressive symptoms.